

SER-AP-ES - hydralazine hydrochloride, hydrochlorothiazide and reserpine tablet, coated
Novartis Pharmaceuticals Corporation

C97-38 (Rev. 1/98) 666496

Ser-Ap-Es[®]

reserpine USP 0.1 mg

hydralazine hydrochloride USP 25 mg

hydrochlorothiazide USP 15 mg

Combination Tablets

Caution: Federal law prohibits dispensing without prescription.

Prescribing Information

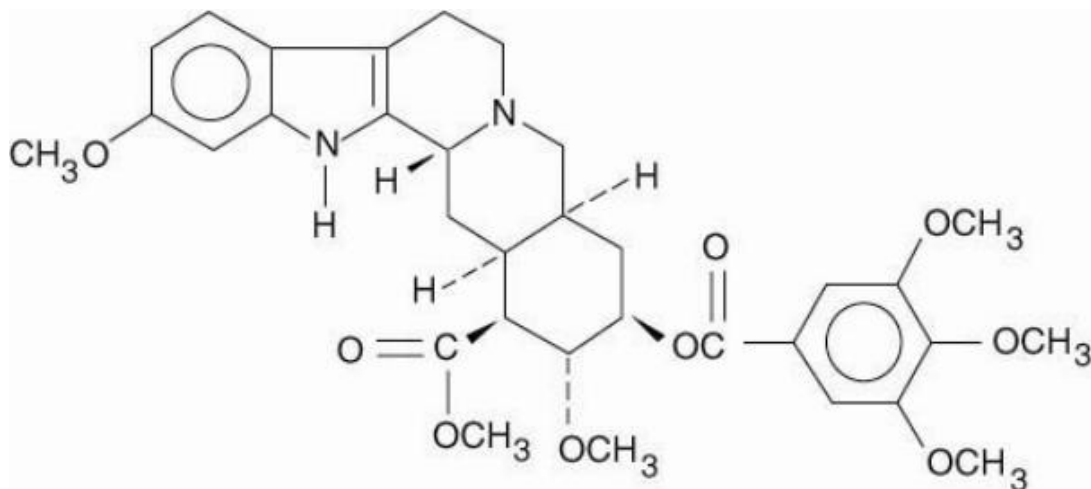
WARNING

This fixed-combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static but must be reevaluated as conditions in each patient warrant.

DESCRIPTION

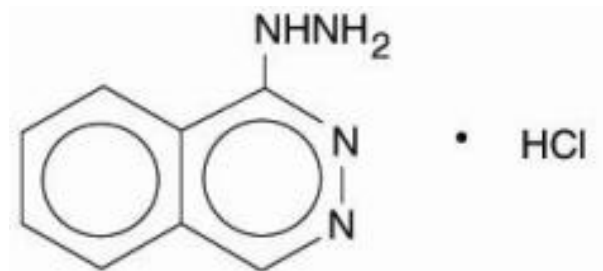
Ser-Ap-Es is an antihypertensive-diuretic combination, available as tablets for oral administration. Each tablet contains Serpasil (reserpine USP), 0.1 mg; Apresoline (hydralazine hydrochloride USP), 25 mg; and Esidrix (hydrochlorothiazide USP), 15 mg.

Reserpine is methyl 18 β -hydroxy-11,17 α -dimethoxy-3 β ,20 α -yohimban-16 β -carboxylate 3,4,5-trimethoxybenzoate (ester), and its structural formula is



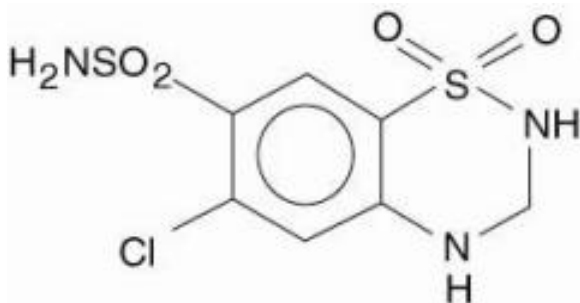
Reserpine USP, a pure crystalline alkaloid of rauwolfia, is a white or pale buff to slightly yellowish, odorless crystalline powder. It darkens slowly on exposure to light, but more rapidly when in solution. It is insoluble in water, freely soluble in acetic acid and in chloroform, slightly soluble in benzene, and very slightly soluble in alcohol and in ether. Its molecular weight is 608.69.

Hydralazine hydrochloride is 1-hydrazinophthalazine monohydrochloride, and its structural formula is



Hydralazine hydrochloride USP is a white to off-white, odorless crystalline powder. It is soluble in water, slightly soluble in alcohol, and very slightly soluble in ether. It melts at about 275°C, with decomposition, and has a molecular weight of 196.64.

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, and its structural formula is



Hydrochlorothiazide USP is a white, or practically white, practically odorless crystalline powder. It is slightly soluble in water; freely soluble in sodium hydroxide solution, in *n*-butylamine, and in dimethylformamide; sparingly soluble in methanol; and insoluble in ether, in chloroform, and in dilute mineral acids. Its molecular weight is 297.73.

Inactive Ingredients. Acacia, FD&C Blue No. 1, FD&C Green No. 3, FD&C Red No. 40, FD&C Yellow No. 6, lactose, polyethylene glycol, starch, stearic acid, and sucrose.

CLINICAL PHARMACOLOGY

Reserpine

Reserpine depletes stores of catecholamines and 5-hydroxytryptamine in many organs, including the brain and adrenal medulla. Most of its pharmacological effects have been attributed to this action. Depletion is slower and less complete in the adrenal medulla than in other tissues.

The depression of sympathetic nerve function results in a decreased heart rate and a lowering of arterial blood pressure. The sedative and tranquilizing properties of reserpine are thought to be related to depletion of catecholamines and 5-hydroxytryptamine from the brain.

Reserpine, like other rauwolfia compounds, is characterized by slow onset of action and sustained effects. Both cardiovascular and central nervous system effects may persist for a period of time following withdrawal of the drug.

Mean maximum plasma levels of 1.54 ng/ml were attained after a median of 3.5 hours in six normal subjects receiving a single oral dose of four 0.25-mg Serpasil tablets.

Bioavailability was approximately 50% of that of a corresponding intravenous dose. Plasma levels of reserpine after intravenous administration declined with a mean half-life of 33 hours. Reserpine is extensively bound (96%) to plasma proteins. No definitive studies on the human metabolism of reserpine have been made.

Hydralazine

Although the precise mechanism of action of hydralazine is not fully understood, the major effects are on the cardiovascular system. Hydralazine apparently lowers blood pressure by exerting a peripheral vasodilating effect through a direct relaxation of vascular smooth muscle. Hydralazine, by altering cellular calcium metabolism, interferes with the calcium movements within the vascular smooth muscle that are responsible for initiating or maintaining the contractile state.

The peripheral vasodilating effect of hydralazine results in decreased arterial blood pressure (diastolic more than systolic); decreased peripheral vascular resistance; and an increased heart rate, stroke volume, and cardiac output. The preferential dilatation of arterioles, as compared to veins, minimizes postural hypotension and promotes the increase in cardiac output. Hydralazine usually increases renin activity in plasma, presumably as a result of increased secretion of renin by the renal juxtaglomerular cells in response to reflex sympathetic discharge. This increase in renin activity leads to the production of angiotensin II, which then causes stimulation of aldosterone and consequent sodium reabsorption. Hydralazine also maintains or increases renal and cerebral blood flow.

Hydralazine is rapidly absorbed after oral administration, and peak plasma levels are reached at 1-2 hours. Plasma levels decline with a half-life of 3-7 hours. Binding to human plasma protein is 87%. Plasma levels of hydralazine vary widely among individuals. Hydralazine is subject to polymorphic acetylation; slow acetylators generally have higher plasma levels of hydralazine and require lower doses to maintain control of blood pressure. Hydralazine undergoes extensive hepatic metabolism; it is excreted mainly in the form of metabolites in the urine.

Administration of hydralazine with food results in higher levels of the drug in plasma.

Hydrochlorothiazide

Thiazides affect the renal tubular mechanism of electrolyte reabsorption. At maximal therapeutic dosage, all thiazides are approximately equal in their diuretic potency. Thiazides increase excretion of sodium and chloride in approximately equivalent amounts. Natriuresis causes a secondary loss of potassium.

The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not affect normal blood pressure.

The onset of action of thiazides occurs in 2 hours, and the peak effect at about 4 hours. The action persists for approximately 6-12 hours. Hydrochlorothiazide is rapidly absorbed, as indicated by peak plasma concentrations 1-2.5 hours after oral administration. Plasma levels of the drug are proportional to dose; the concentration in whole blood is 1.6-1.8 times higher than in plasma. Thiazides are eliminated rapidly by the kidney. After oral administration of 25- to 100-mg doses of hydrochlorothiazide, 72%-97% of the dose

is excreted in the urine, indicating dose-independent absorption. Hydrochlorothiazide is eliminated from plasma in a biphasic fashion with a terminal half-life of 10-17 hours. Plasma protein binding is 67.9%. Plasma clearance is 15.9-30.0 L/hr; volume of distribution is 3.6-7.8 L/kg.

Gastrointestinal absorption of hydrochlorothiazide is enhanced when administered with food. Absorption is decreased in patients with congestive heart failure, and the pharmacokinetics are considerably different in these patients.

INDICATIONS AND USAGE

Hypertension (see boxed WARNING).

CONTRAINDICATIONS

Reserpine

Hypersensitivity to reserpine; mental depression or history of mental depression (especially with suicidal tendencies); active peptic ulcer, ulcerative colitis; patients receiving electroconvulsive therapy.

Hydralazine

Hypersensitivity to hydralazine; coronary artery disease; mitral valvular rheumatic heart disease.

Hydrochlorothiazide

Anuria; hypersensitivity to this or other sulfonamide-derived drugs.

WARNINGS

Reserpine

Reserpine may cause mental depression. Recognition of depression may be difficult because this condition may often be disguised by somatic complaints. The drug should be discontinued at first signs of depression such as despondency, early morning insomnia, loss of appetite, impotence, or self-deprecation. Drug-induced depression may persist for several months after drug withdrawal and may be severe enough to result in suicide.

Hydralazine

In a few patients hydralazine may produce a clinical picture simulating systemic lupus erythematosus including glomerulonephritis. In such patients hydralazine should be discontinued unless the benefit-to-risk determination requires continued antihypertensive therapy with this drug. Signs and symptoms usually regress when the drug is discontinued, but residua have been detected many years later. Long-term treatment with steroids may be necessary. (See PRECAUTIONS, Laboratory Tests.)

Hydrochlorothiazide

Thiazides should be used with caution in patients with severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte imbalance may precipitate hepatic coma.

Thiazides may add to or potentiate the action of other antihypertensive drugs. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.

Sensitivity reactions are more likely to occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

PRECAUTIONS

General

Reserpine

Since reserpine increases gastrointestinal motility and secretion, it should be used cautiously in patients with a history of peptic ulcer, ulcerative colitis, or gallstones (biliary colic may be precipitated).

Caution should be exercised when treating hypertensive patients with renal insufficiency, since they adjust poorly to lowered blood pressure levels.

Preoperative withdrawal of reserpine does not assure that circulatory instability will not occur. It is important that the anesthesiologist be aware of the patient's drug intake and consider this in the overall management, since hypotension has occurred in patients receiving rauwolfia preparations. Anticholinergic and adrenergic drugs (e.g., metaraminol, norepinephrine) have been employed to treat adverse vagocirculatory effects.

Hydralazine

Myocardial stimulation produced by hydralazine can cause anginal attacks and ECG changes indicative of myocardial ischemia. The drug has been implicated in the production of myocardial infarction. It must, therefore, be used with caution in patients with suspected coronary artery disease.

The “hyperdynamic” circulation caused by hydralazine may accentuate specific cardiovascular inadequacies. For example, hydralazine may increase pulmonary artery pressure in patients with mitral valvular disease. The drug may reduce the pressor responses to epinephrine. Postural hypotension may result from hydralazine but is less common than with ganglionic blocking agents. It should be used with caution in patients with cerebral vascular accidents.

In hypertensive patients with normal kidneys who are treated with hydralazine, there is evidence of increased renal blood flow and a maintenance of glomerular filtration rate. In some instances where control values were below normal, improved renal function has been noted after administration of hydralazine. However, as with any antihypertensive agent, hydralazine should be used with caution in patients with advanced renal damage.

Peripheral neuritis, evidenced by paresthesia, numbness, and tingling, has been observed. Published evidence suggests that hydralazine has an antipyridoxine effect and that pyridoxine should be added to the regimen if symptoms develop.

Hydrochlorothiazide

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance, namely hyponatremia, hypochloremic alkalosis, and hypokalemia (see Laboratory Tests and Drug/Drug Interactions). Warning signs are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbance, such as nausea or vomiting. Thiazide diuretics have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Hypokalemia may develop, especially in cases of brisk diuresis or severe cirrhosis. Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Hypokalemia may be avoided or treated by use of potassium supplements or foods with a high potassium content.

Any chloride deficit is generally mild and usually does not require specific treatment, except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In cases of actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Latent diabetes may become manifest during thiazide administration (see Drug/Drug Interactions).

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident, withholding or discontinuing diuretic therapy should be considered.

Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. The common complications of hyperparathyroidism, such as renal lithiasis, bone resorption, and peptic ulceration, have not been seen.

Information for Patients

Patients should be informed of possible side effects and advised to take the medication regularly and continuously as directed.

Laboratory Tests

Hydralazine

Complete blood counts and antinuclear antibody titer determinations are indicated before and periodically during prolonged therapy with hydralazine even though the patient is asymptomatic. These studies are also indicated if the patient develops arthralgia, fever, chest pain, continued malaise, or other unexplained signs or symptoms.

A positive antinuclear antibody titer requires that the physician carefully weigh the implications of the test results against the benefits to be derived from antihypertensive therapy with a combination drug containing hydralazine.

Blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura, have been reported. If such abnormalities develop, therapy should be discontinued.

Hydrochlorothiazide

Initial and periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids.

Drug/Drug Interactions

Reserpine

MAO inhibitors should be avoided or used with extreme caution.

Reserpine should be used cautiously with digitalis and quinidine, since cardiac arrhythmias have occurred with rauwolfia preparations.

Concurrent use of tricyclic antidepressants may decrease the antihypertensive effect of reserpine (see CONTRAINDICATIONS).

Concurrent use of reserpine and direct or indirect-acting sympathomimetics should be closely monitored. The action of direct-acting amines (epinephrine, isoproterenol, phenylephrine, metaraminol) may be prolonged when given to patients taking reserpine. The action of indirect-acting amines (ephedrine, tyramine, amphetamines) is inhibited.

Hydralazine

MAO inhibitors should be used with caution in patients receiving hydralazine. When other potent parenteral antihypertensive drugs, such as diazoxide, are used in combination with hydralazine, patients should be continuously observed for several hours for any excessive fall in blood pressure. Profound hypotensive episodes may occur when diazoxide injections and hydralazine are used concomitantly.

Hydrochlorothiazide

Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

Hypokalemia may develop during concomitant use of steroids or ACTH.

Insulin requirements in diabetic patients may be increased, decreased, or unchanged.

Thiazides may decrease arterial responsiveness to norepinephrine, but not enough to preclude effectiveness of the pressor agent for therapeutic use.

Thiazides may increase the responsiveness to tubocurarine.

Lithium renal clearance is reduced by thiazides, increasing the risk of lithium toxicity.

There have been rare reports in the literature of hemolytic anemia occurring with the concomitant use of hydrochlorothiazide and methyldopa.

Concurrent administration of some nonsteroidal anti-inflammatory agents may reduce the diuretic, natriuretic and antihypertensive effects of thiazide diuretics.

Cholestyramine and colestipol resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively.

Drug/Laboratory Test Interactions

Thiazides may decrease serum levels of protein-bound iodine without signs of thyroid disturbance. Ser-Ap-Es should be discontinued before tests for parathyroid function are made (see General, Hydrochlorothiazide, Calcium excretion).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity, and fertility studies in animals have not been conducted with Ser-Ap-Es.

Reserpine

Animal Tumorigenicity

Rodent studies have shown that reserpine is an animal tumorigen, causing an increased incidence of mammary fibroadenomas in female mice, malignant tumors of the seminal vesicles in male mice, and malignant adrenal medullary tumors in male rats. These findings arose in 2-year studies in which the drug was administered in the feed at concentrations of 5 and 10 ppm-about 100 to 300 times the usual human dose. The breast neoplasms are thought to be related to reserpine's prolactin-elevating effect. Several other prolactin-elevating drugs have also been associated with an increased incidence of mammary neoplasia in rodents.

The extent to which these findings indicate a risk to humans is uncertain. Tissue culture experiments show that about one third of human breast tumors are prolactin-dependent in vitro, a factor of considerable importance if the use of the drug is contemplated in a patient with previously detected breast cancer. The possibility of an increased risk of breast cancer in reserpine users has been studied extensively; however, no firm conclusion has emerged. Although a few epidemiologic studies have suggested a slightly increased risk (less than twofold in all studies except one) in women who have used reserpine, other studies of generally similar design have not confirmed this. Epidemiologic studies conducted using other drugs (neuroleptic agents) that, like reserpine, increase prolactin levels and therefore would be considered rodent mammary carcinogens have not shown an association between chronic administration of the drug and human mammary tumorigenesis. While long-term clinical observation has not suggested such an association, the available evidence is considered too limited to be conclusive at this time. An association of reserpine intake with pheochromocytoma or tumors of the seminal vesicles has not been explored.

Hydralazine

In a lifetime study in Swiss albino mice, there was a statistically significant increase in the incidence of lung tumors (adenomas and adenocarcinomas) of both male and female mice given hydralazine continuously in their drinking water at a dosage of about 250 mg/kg/day (about 80 times the maximum recommended human dose). In a 2-year carcinogenicity study of rats given hydralazine by gavage at dose levels of 15, 30, and 60 mg/kg/day (approximately 5 to 20 times the recommended human daily dosage), microscopic examination of the liver revealed a small, but statistically significant, increase in benign neoplastic nodules in male and female rats from the high-dose group and in female rats from the intermediate-dose group. Benign interstitial cell tumors of the testes were also significantly increased in male rats from the high-dose group. The tumors observed are common in aged rats and a significantly increased incidence was not observed until 18 months of treatment. Hydralazine was shown to be mutagenic in bacterial systems (Gene Mutation and DNA Repair) and in one of two rat and one rabbit hepatocyte in vitro DNA repair studies. Additional in vivo and in vitro studies using lymphoma cells, germinal cells, and fibroblasts from mice, bone marrow cells from Chinese hamsters and fibroblasts from human cell lines did not demonstrate any mutagenic potential for hydralazine.

The extent to which these findings indicate a risk to man is uncertain. While long-term clinical observation has not suggested that human cancer is associated with hydralazine use, epidemiologic studies have so far been insufficient to arrive at any conclusions.

Fertility studies in animals have not been conducted with hydralazine.

Hydrochlorothiazide

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses up to approximately 600 mg/kg/day) or in male and female rats (at doses up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic in in vitro assays using strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 of *Salmonella typhimurium* (Ames assay) and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or in in vivo assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the in vitro CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 µg/mL, and in the *Aspergillus nidulans* nondisjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses up to 100 and 4 mg/kg/day, respectively, prior to mating, and throughout gestation.

Pregnancy

Teratogenic Effects. Pregnancy Category C

Animal reproduction studies have not been conducted with Ser-Ap-Es.

Reserpine

Reserpine administered parenterally has been shown to be teratogenic in rats at doses up to 2 mg/kg and to have an embryocidal effect in guinea pigs given dosages of 0.5 mg daily.

Hydralazine

Animal studies indicate that hydralazine is teratogenic in mice at 20-30 times the maximum daily human dose of 200-300 mg and possibly in rabbits at 10-15 times the maximum daily human dose, but that it is nonteratogenic in rats. Teratogenic effects observed were cleft palate and malformations of facial and cranial bones.

Hydrochlorothiazide

Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 and 1000 mg/kg/day, respectively, provided no evidence of harm to the fetus. There are, however, no adequate and well-controlled studies of Ser-Ap-Es in pregnant women. Because animal reproduction studies are not always predictive of human response, this combination drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects

Reserpine

Reserpine crosses the placental barrier and increased respiratory tract secretions, nasal congestion, cyanosis, and anorexia may occur in neonates of mothers treated with reserpine.

Hydrochlorothiazide

Thiazides also cross the placental barrier and appear in cord blood, and there is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Nursing Mothers

Reserpine is excreted in maternal breast milk, and increased respiratory tract secretions, nasal congestion, cyanosis, and anorexia may occur in breast-fed infants. Thiazides are also excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants and the potential for tumorigenicity shown for reserpine in animal studies, a decision should be made whether to discontinue nursing or to discontinue Ser-Ap-Es, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of the combination drug in pediatric patients have not been established.

ADVERSE REACTIONS

Adverse reactions are usually reversible upon reduction of dosage or discontinuation of Ser-Ap-Es. Whenever adverse reactions are moderate or severe, it may be necessary to discontinue the drug.

The following adverse reactions have been observed, but there has not been enough systematic collection of data to support an estimate of their frequency. Consequently the reactions are categorized by organ system and are listed in decreasing order of severity and not frequency.

Reserpine

The following have been observed with rauwolfia preparations:

Digestive: Vomiting, diarrhea, nausea, anorexia, dryness of mouth, hypersecretion.

Cardiovascular: Arrhythmias (particularly when used concurrently with digitalis or quinidine), syncope, angina-like symptoms, bradycardia, edema.

Respiratory: Dyspnea, epistaxis, nasal congestion.

Neurologic: Rare parkinsonian syndrome and other extrapyramidal tract symptoms; dizziness; headache; paradoxical anxiety; depression; nervousness, nightmares; dull sensorium; drowsiness.

Musculoskeletal: Muscular aches.

Genitourinary: Pseudolactation, impotence, dysuria, gynecomastia, decreased libido, breast engorgement

Metabolic: Weight gain.

Special Senses: Deafness, optic atrophy, glaucoma, uveitis, conjunctival injection.

Hypersensitive Reactions: Purpura, rash, pruritus.

Hydralazine

Digestive: Hepatitis, paralytic ileus, vomiting, diarrhea, nausea, constipation, anorexia.

Cardiovascular: Angina pectoris, hypotension, paradoxical pressor response, tachycardia, palpitations, edema, flushing.

Respiratory: Dyspnea, nasal congestion.

Neurologic: Psychotic reactions characterized by depression, disorientation, or anxiety; peripheral neuritis, evidenced by paresthesia, numbness, and tingling; tremors; dizziness, headache.

Musculoskeletal: Muscle cramps, arthralgia.

Genitourinary: Difficulty in urination.

Hematologic: Blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis; lymphadenopathy; splenomegaly, eosinophilia.

Special Senses: Conjunctivitis, lacrimation.

Hypersensitive Reactions: Purpura, fever, urticaria, rash, pruritus, chills.

Hydrochlorothiazide

Digestive: Pancreatitis, jaundice (intrahepatic cholestatic), sialadenitis, vomiting, diarrhea, cramping, nausea, gastric irritation, constipation, anorexia.

Cardiovascular: Orthostatic hypotension (may be potentiated by alcohol, barbiturates, or narcotics).

Neurologic: Vertigo, dizziness, transient blurred vision, headache, paresthesia, xanthopsia, weakness, restlessness.

Musculoskeletal: Muscle spasm.

Hematologic: Aplastic anemia, agranulocytosis, leukopenia, thrombocytopenia.

Metabolic: Hyperglycemia, glycosuria, hyperuricemia.

Hypersensitive Reactions: Necrotizing angitis, Stevens-Johnson syndrome, respiratory distress including pneumonitis and pulmonary edema, purpura, urticaria, rash, photosensitivity.

OVERDOSAGE

Acute Toxicity

No deaths due to acute poisoning with Ser-Ap-Es have been reported. Oral LD₅₀'s in animals (mg/kg): rats, 397; mice, 272.

Signs and Symptoms

Reserpine

The clinical picture of acute poisoning is characterized chiefly by signs and symptoms due to the reflex parasympathomimetic effect of reserpine.

Impairment of consciousness may occur and may range from drowsiness to coma, depending upon the severity of overdosage. Flushing of the skin, conjunctival injection, and pupillary constriction are to be expected. Hypotension, hypothermia, central respiratory depression, and bradycardia may develop in cases of severe overdosage. Increased salivary and gastric secretion and diarrhea may also occur.

Hydralazine

Signs and symptoms of overdosage include hypotension, tachycardia, headache, and generalized skin flushing.

Complications can include myocardial ischemia and subsequent myocardial infarction, cardiac arrhythmia, and profound shock.

Hydrochlorothiazide

The most prominent feature of poisoning is acute loss of fluid and electrolytes.

Cardiovascular: Tachycardia, hypotension, shock.

Neuromuscular: Weakness, confusion, dizziness, cramps of the calf muscles. paresthesia, fatigue, impairment of consciousness.

Digestive: Nausea, vomiting, thirst.

Renal: Polyuria, oliguria, or anuria (due to hemoconcentration).

Laboratory Findings: Hypokalemia, hyponatremia, hypochloremia, alkalosis; increased BUN (especially in patients with renal insufficiency).

Combined Poisoning: Signs and symptoms may be aggravated or modified by concomitant intake of antihypertensive medication, barbiturates, digitalis (hypokalemia), corticosteroids, narcotics, or alcohol.

Treatment

There is no specific antidote.

The gastric contents should be evacuated, taking adequate precautions against aspiration and for protection of the airway. An activated charcoal slurry may be instilled if conditions permit. Dialysis may not be effective for elimination of Ser-Ap-Es because of its plasma protein binding (see CLINICAL PHARMACOLOGY).

These manipulations may have to be omitted or carried out after cardiovascular status has been stabilized, since they might precipitate cardiac arrhythmias or increase the depth of shock.

If hypotension or shock occurs, the patient's legs should be kept raised and lost fluid and electrolytes (potassium, sodium) should be replaced.

Support of the cardiovascular system is of primary importance in suspected hydralazine overdosage. If possible, vasopressors should not be given, but if a vasopressor is required, care should be taken not to precipitate or aggravate cardiac arrhythmia. Tachycardia responds to beta blockers. Digitalization may be necessary.

If hypotension is severe enough to require treatment with a vasopressor, one having a direct action upon vascular smooth muscle (e.g., phenylephrine, levarterenol, metaraminol) should be used to treat the symptomatic effects of reserpine overdosage.

Fluid and electrolyte balance (especially serum potassium) and renal function should be monitored until conditions become normal. Since reserpine is long-acting, the patient should be observed carefully for at least 72 hours.

DOSAGE AND ADMINISTRATION

Dosage should be determined by individual titration (see boxed WARNING). Dosage regimens that exceed 0.25 mg of reserpine per day are not recommended.

HOW SUPPLIED

Tablets – round, salmon pink, dry-coated (imprinted CIBA 71) 0.1 mg of reserpine, 25 mg of hydralazine hydrochloride, 15 mg of hydrochlorothiazide

Bottles of 100..... NDC 0083-0071-30

Bottles of 1000.....NDC 0083-0071-40

Do not store above 30°C (86°F). Dispense in tight, light-resistant container (USP).

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